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Characteristics of the carotid baroreflex in man during normal and flow-restricted exercise

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Eight subjects were studied in the supine position at rest, during normal dynamic leg exercise (control exercise) and with blood-flow restriction in the working legs (flow-restricted exercise). Graded muscle blood-flow restriction was accomplished by applying a supra-atmospheric pressure of 50 mmHg to the working legs. During incremental-load exercise, flow restriction reduced exercise performance and peak heart rate by 36% and 13%, respectively. The function of the cardiac branch of the carotid baroreflex was studied over its full operational range, at rest and during constant-load control and flow-restricted exercise, by measuring R-R intervals during application of pulse-synchronous graded pressures (40 to −65 mmHg) in a neck-chamber device. Heart rate and arterial pressure were higher during flow-restricted than control exercise, indicating that the flow restriction activated the muscle chemoreflex. Raising the carotid transmural pressure (systolic arterial pressure minus neck-chamber pressure) was accompanied by increasing R-R intervals in all conditions. The set point (point of baseline carotid transmural pressure and R-R interval) coincided with the midportion of the pressure-response curve at rest and with the threshold point of the curve during exercise. The maximal rate of change in relative R-R intervals and the corresponding carotid transmural pressure range were higher during control exercise than at rest and highest during flow-restricted exercise, indicating that exercise and especially flow-restricted exercise increased carotid baroflex sensitivity, and shifted the carotid baroreflex optimal buffering range to higher pressures. The results suggest that the carotid baroflex attenuates exercise heart rate increases mediated by the muscle chemoreflex and/or by central command.

Key words: arterial baroreflex pressure-response relation, ischaemic exercise.

It has recently been found that cardiovascular responses to dynamic leg exercise in man are exaggerated by experimentally-induced graded restriction of blood flow in the exercising muscles. Thus, heart rate (HR) and arterial pressure were higher at any given work load when supine incremental-load cycling was performed under moderately restricted muscle blood-flow than free-flow conditions (Eiken & Bjurstedt 1987). The exaggerated pressor response is attributable to the muscle chemoreflex (for ref. see Mitchell & Schmidt 1983) and/or to augmented central command (Victor & Seals 1989). It was also found that peak HR was lower during flow-restricted (FR) exercise than during free-flow exercise, whereas systolic arterial pressure (SAP) attained similar peak values (Eiken & Bjurstedt 1987). In flow-restricted

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exercise, the reduction in peak HR as compared with that in control exercise may conceivably have been caused by baroreflex influence from the exaggerated pressor response. Static exercise, on the other hand, which is also known to activate the muscle chemoreflex (cf Mitchell & Schmidt 1983) and/or augment central command (Victor *et al.* 1989), has been reported to considerably suppress the arterial baroreflex gain (Cunningham *et al.* 1972, Mancia *et al.* 1978).

The present study was undertaken to investigate the characteristics of the carotid arterial baroreflex as influenced by normal and ischaemic dynamic exercise. Graded blood-flow restriction in the exercising muscles was induced by applying a supra-atmospheric pressure to the legs during supine cycling (Leg Positive Pressure; LPP). Carotid baroreceptors were stimulated and unloaded by pulse-synchronous, step-wise changes in the atmospheric pressure surrounding the neck (cf Sprenkle *et al.* 1986).

METHODS

Eight healthy male subjects took part in the study. Mean (range) age, height and weight were 28 (23–35) years, 173 (167–178) cm and 69 (63–81) kg, respectively. Before giving informed consent the subjects were thoroughly acquainted with the experimental procedures. The design of the investigation was approved by the Human Ethics Committee of Simon Fraser University.

The experimental arrangements that were used to induce graded blood-flow restriction during exercise have been described by Eiken & Bjurstedt (1987). Briefly, the experiments were conducted with the subject positioned supine in the opening to a large pressure chamber, with the legs inside the chamber and the feet strapped to the pedals of a mechanically braked cycle ergometer (Monark). The axis of the pedals was at the level of the heart. Hermetic sealing of the chamber was accomplished by using a rubber diaphragm with two holes and short self-sealing sleeves for the legs. The subject was provided with shoulder supports to avoid craniad displacement of the body as the chamber pressure was increased.

Carotid baroreceptor manipulation was achieved by means of a neck-chamber device, described in detail by Sprenkle *et al.* (1986). The stimulus profile consisted of raising neck chamber pressure to 40 mmHg for five heart beats, followed by successive 15 mmHg R-wave triggered decrements to −65 mmHg. This produced a series of stair-stepped neck pressure reductions that were superimposed on seven successive carotid arterial pulses. To avoid respiration related variations of cardiac vagal outflow (cf Eckberg *et al.* 1988), neck pressure changes were applied only during breath holding at the mid-expiratory level. All subjects were trained to hold their breath without performing a Valsalva manoeuvre both at rest and during exercise. Neck-chamber pressure was measured continuously during the neck-pressure profiles (cf. Sprenkle *et al.* 1986).

HR was derived from electrocardiographic recordings using a bipolar precordial lead. SAP was measured sphygmomanometrically using an automatic blood-pressure recorder (UA-251, Japan). Diastolic arterial pressure (DAP) was measured by the volume-clamp technique (Penaz 1973) using a Finapres 2350 (cf Wesseling *et al.* 1982). The cuff was placed on the distal phalanx of the third digit. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the DAP. The level of the heart was used as the point of reference for the arterial pressure recordings. The rationale behind using different methods in the determinations of SAP and DAP is that during muscular exercise, SAP but not DAP is measured accurately by the sphygmomanometrical method (Kaijser 1987), whereas DAP but not SAP is measured accurately by the Finapres (Idema *et al.* 1989).

Experimental protocol

Incremental-load exercise. Each subject performed exhaustive incremental-load exercise on two different occasions, once with normal atmospheric pressure in the chamber (control) and once with a supra-atmospheric chamber pressure of 50 mmHg (LPP). The two trials were separated by a minimum of 48 h and the order in which they were carried out was alternated among subjects. Each trial started with a 4-min warm-up period of loadless pedalling after which the work rate was increased by 30 W every other min until the subject was unable to maintain the required pedalling frequency (60 rpm). Peak work rate was defined as the highest work rate that the subject could sustain for the full 2-min period. HR was measured throughout the experiments.

Carotid baroreflex manipulation. In addition to the incremental-load tests, each subject performed one control and one LPP (+50 mmHg) experiment during which the carotid baroreflex (CBR) was manipulated by means of neck-pressure manoeuvres. These trials were separated by a minimum of 48 h and the order in which they were carried out was alternated among subjects. Each experiment consisted of 14 min of motionless rest and 14 min of constant-load pedalling (60 r.p.m.) at 30% of each individuals control peak work rate. In the LPP condition this work rate corresponded to 43% (range: 40–50%) of the LPP peak work rate. Each neck-pressure manoeuvre was conducted every other min starting from min 4 of the rest and exercise periods, respectively. Thus, five

neck-pressure manoeuvres were performed at rest as well as during exercise in both the control and LPP conditions. SAP, DAP and HR were measured immediately prior to the neck-pressure manoeuvres.

Analysis of data. Recordings obtained during or in connection with the five neck-pressure manoeuvres, for each subject, were averaged for each experimental treatment: control rest, control exercise, LPP rest and LPP exercise. Carotid transmural pressure (CTP) was derived by subtracting neck-chamber pressure from SAP. The sensitivity and the optimal buffering pressure of the CBR were determined from the R-R intervals and CTP values obtained during neck-pressure manoeuvres in the following way. Relative R-R interval was plotted as a function of CTP for each step of the neck-pressure manoeuvre. The baseline R-R, from the four beats immediately prior to a manoeuvre, was defined as 100%. Thereafter, a fourth-order polynoma (i.e.: $(f(x) = a + bx + cx^2 + dx^3 + ex^4)$ was fitted to the data points by use of an iterative least-square method. The best-fit function thus obtained was differentiated and the maximum derivative and its corresponding CTP value were defined as CBR sensitivity and CBR optimal buffering pressure, respectively.

The significance of inter-condition differences was evaluated employing analysis of variance.

RESULTS

Incremental-load exercise

Exercise performance was considerably impaired by LPP. The peak work rate in the LPP condition (mean ± SD = 146 ± 18 W) was 64% of that in the control condition (225 ± 9 W). The time until exhaustion was reduced ($P < 0.001$) from 15.5 ± 1.7 to 10.4 ± 1.2 min. Resting HR was unaffected by LPP. The exercise HR response, however, was exaggerated by LPP so that HR was higher ($P < 0.05$) at any given work rate in the LPP than in the control condition. Nevertheless, peak HR was considerably lower ($P < 0.001$) during LPP (164 ± 12 beats min^{-1}) than control exercise (185 ± 11 beats min^{-1}).

Carotid baroreflex manipulation

Table 1 shows baseline values for SAP, MAP, DAP and HR at rest and during constant-load exercise in the two conditions. It can be seen that at rest SAP was higher (14 mmHg; $P < 0.05$) in the LPP than in the control condition. Resting values for DAP, MAP and HR were unaffected by LPP. During exercise SAP, MAP and DAP were increased ($P < 0.01$) 32, 25 and 21 mmHg, respectively, by LPP. Likewise, exercise HR was 9 beats min^{-1} higher ($P < 0.05$) in the LPP than in the control condition.

In these experiments, neck-pressure manoeuvres resulted in increasing R-R intervals (decreasing HR) with increasing CTP in all conditions (Fig. 1). Both at control rest and at LPP rest the set point (i.e. the point of baseline

Table 1. Effect of Leg Positive Pressure (LPP) on systolic, mean and diastolic arterial pressures (SAP, MAP, DAP) and on heart rate (HR) at rest and during exercise.

Variable	Rest	Exercise
SAP (mmHg)		
Control	117 ± 7	144 ± 11
LPP	131 ± 16	176 ± 13
Difference	14*	32**
MAP (mmHg)		
Control	90 ± 8	104 ± 11
LPP	101 ± 12	129 ± 13
Difference	11 n.s.	25**
DAP (mmHg)		
Control	77 ± 10	84 ± 10
LPP	87 ± 12	105 ± 15
Difference	10 n.s.	21**
HR (beats min^{-1})		
Control	64 ± 11	101 ± 11
LPP	68 ± 10	110 ± 17
Difference	4 n.s.	9*

Values are means ± SD. $n = 8$; ** $P < 0.01$; * $P < 0.05$; n.s. = non significant.

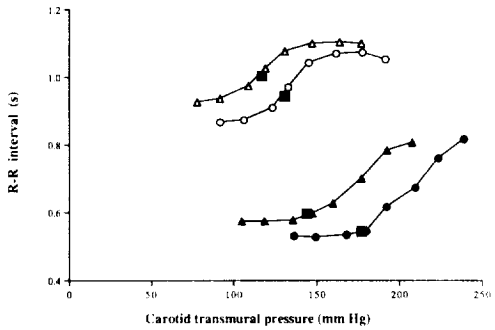

Fig. 1. R-R interval as a function of carotid transmural pressure in neck-pressure experiments at rest and during exercise in the control and LPP conditions. Control rest (△), LPP rest (○), Control exercise (▲), LPP exercise (●). The set point (see text) is indicated for each curve (■). Values are means; $n = 8$.

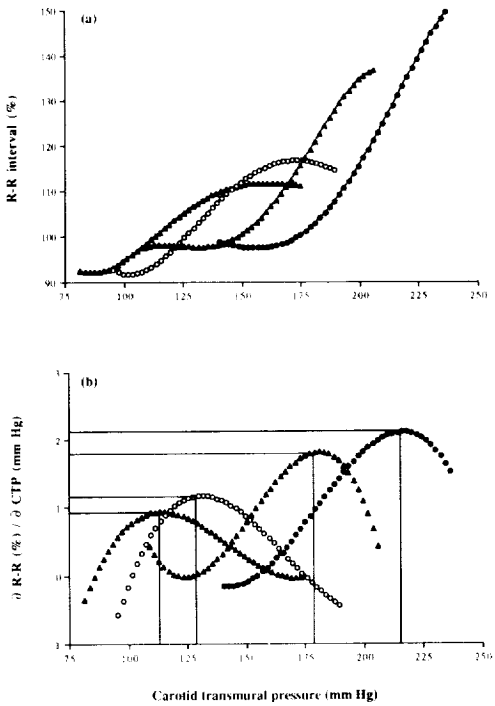

Fig. 2. Relative R-R interval (a) and differentiated relative R-R interval (b) as functions of carotid transmural pressure (CTP) in neck-pressure experiments at rest and during exercise in the control and LPP conditions. Control rest (△), LPP rest (○), Control exercise (▲), LPP exercise (●). CBR sensitivity and CBR optimal buffering pressure (see text) are indicated in differentiated curves by horizontal and vertical lines, respectively. All curves represent best-fit functions of averaged data ($n = 8$).

R-R and CTP values) coincided with the midportion of the pressure-response curve. During control and LPP exercise the set points were closer to the pressure-response thresholds. Figure 2 shows the best-fit functions of relative R-R intervals as well as the differentiated R-R curves as functions of the CTP. As defined by the differentiated R-R curves the CBR sensitivity was higher ($P < 0.05$) for the control exercise condition (best-fit function of averaged data: $1.73\,\delta\%/\delta$ mmHg) than at rest for the control ($0.86\,\delta\%/\delta$ mmHg) or LPP conditions ($1.10\,\delta\%/\delta$ mmHg). It was even higher ($P < 0.05$) for the LPP exercise condition ($2.05\,\delta\%/\delta$ mmHg). The difference between resting values was not significant. Further, exercise and especially LPP exercise, shifted the pressure-response curve along the pressure axis. The optimal buffering pressure was higher ($P < 0.01$) during control exercise (179 mmHg) than for control rest (111 mmHg) or LPP rest (130 mmHg), and was highest ($P < 0.01$) during LPP exercise (214 mmHg). The difference between the resting values was significant ($P < 0.05$).

DISCUSSION

The purpose of the investigation was to study the characteristics of the carotid baroreflex as influenced by normal and ischaemic dynamic exercise.

The presently applied pulse-synchronous neck-pressure changes (cf. Sprenkle *et al.* 1986) enabled us to study the carotid baroreflex response over most of its full operational range both at rest and during exercise. This is imperative when determining the gain and the operational pressure range of the reflex (cf. Abboud & Thames 1983). Also, superimposing the neck-pressure changes on the arterial pulse waves is a more physiological means of stimulating the carotid baroreceptors than applying a static change in neck-pressure (cf. Eckberg 1977). However, the brevity (ranging from 6.6 s during LPP exercise to 11.0 s during control rest) and/or the complexity of the neck-pressure profile limited our study to the cardiac branch of the reflex response. Trial experiments revealed that arterial pressure did not change significantly during the course of a neck-pressure profile. This is in agreement with previous findings (Sprenkle *et al.* 1986).

Stimulation of the muscle chemoreflex and/or augmentation in central command was achieved by restriction of blood flow in exercising muscles by exposure of the legs to an increased ambient pressure of 50 mmHg (cf. Eiken & Bjurstedt 1987). Sundberg & Kaijser (personal communication) recently verified that blood flow in exercising leg muscles is substantially reduced by LPP of 50 mmHg. The mechanisms underlying such restriction of leg blood flow during cycle ergometry has been described in detail elsewhere (Eiken 1987). Briefly, muscle perfusion pressure is decreased by LPP because the external pressure is transmitted to the muscle tissue (cf. Thron *et al.* 1967) such that local venous pressure rises until it just exceeds the elevated tissue pressure (cf. Roddie & Shepherd

1957). In close agreement with previous findings (Eiken & Bjurstedt 1987), the LPP-induced decrease in muscle perfusion pressure, thus accomplished restricted local blood flow during the exhaustive exercise trials to the degree that the peak work rate that could be attained in the LPP condition was only 64% of control peak work rate. In the present experiments, exercise at a constant work rate of 30% of the peak work rate attained in 'free-flow' exercise resulted in exaggerated HR and arterial pressure responses when LPP was applied, implying that in this condition even work rates of relatively low intensity are associated with a blood-flow error sufficiently great to activate muscle chemosensors (cf Mitchell & Schmidt 1983) and/or to exaggerate central command (cf. Victor *et al.* 1989; Victor & Seals 1989).

Our results showed that the sensitivity and the optimal buffering pressure of the carotid baroreflex was higher during control exercise than at rest and even higher during LPP exercise. That the sigmoid pressure-response relationship is shifted to higher operational pressures in exercising humans is a novel finding, but is in conformity with the concept of an acute reset capability of the arterial baroreflex (cf. Korner 1979, Coleridge *et al.* 1981, Dorward *et al.* 1982, Munch *et al.* 1983, Heesch *et al.* 1984, Undesser *et al.* 1984, Kasting *et al.* 1987). It is noteworthy, in this connection, that the pressure-response relationship was elevated by LPP also in the resting condition (see Fig. 3). At rest, LPP increases SAP by augmenting the stroke volume. The LPP-induced exaggeration of the exercise pressor response in contrast, is due to augmentations in HR and peripheral resistance while stroke volume attains similar values as during control exercise (Eiken & Bjurstedt 1987). Thus, irrespective of its cause, an acute sustained increase in the carotid transmural pressure will shift the carotid baroreflex pressure-response relationship to higher operational pressures.

Our finding that exercise increased CBR sensitivity may also be attributable to baroreceptor resetting. Heesch *et al.* (1984) and Undesser *et al.* (1984) found, when recording nerve-discharge patterns from arterial baroreceptors, that an acute increase in transmural pressure not only increased the discharge threshold but also increased the slope of the pressure-discharge curve. Heesch *et al.* suggested that when a baroreceptor area is biased by increased transmural pressure, the low-threshold baroreceptor units reset to a greater extent than do the high-pressure units, which, in turn, leads to an increased gain (i.e. slope of pressure-discharge curve) of the overall reflex.

That muscular exercise and especially flow-restricted exercise increases the gain of the carotid baroreflex is at variance with some observations previously reported in the literature. It has been suggested that the baroreflex gain is either unaltered (Bevegård & Shepherd 1966, Robinson *et al.* 1966) or severely reduced (Cunningham *et al.* 1972, Mancia *et al.* 1978) by muscular exercise. The discrepancy between our interpretation and those of others may be ascribed to different means of determining the reflex gain. Thus, in contrast to the present experiments, previous studies have determined the gain of the arterial and/or carotid baroreflex in exercising man by investigating only a portion of the sigmoid pressure-response relationship (cf. Bevegård & Shepherd 1966, Robinson *et al.* 1966, Cunningham *et al.* 1972, Mancia *et al.* 1978). Further, neither Cunningham *et al.* (1972) nor Mancia *et al.* (1978) accounted for the exercise induced decreases in R-R interval when determining the baroreflex gain. Our finding of an augmented cardio-decelerating capacity of the carotid baroreflex in the face of increased muscle chemosensor activity and/or increased central command may explain why peak HR was lower during LPP exercise than during control exercise. It seems likely that during LPP exercise a HR increase induced by muscle ischaemia was attenuated by arterial baroreflex stimulation as triggered by an exaggerated increase in SAP. That the exercise response for arterial pressure is greatly exaggerated by LPP exposure is evident from the present results as well as from previous experiments (Eiken & Bjurstedt 1987).

In this connection it should be mentioned that in patients with intermittent claudication the peak heart rate during exhaustive dynamic leg exercise is substantially lower before than after reconstructive surgery of the obstructed leg arteries (Pernow *et al.* 1975). It has been shown that the exercise pressor-response is exaggerated in patients with intermittent claudication (Lorentsen 1972). That arterial baroreflex stimulation may attenuate the pressor response induced by ischaemic exercise is further supported by a recent study in dogs in which it was

found that chronic denervation of arterial baroreceptors brought about an exaggerated pressor response during flow-restricted exercise (Sheriff *et al.* 1990).

The present results suggest that the carotid baroreflex played an important role in the control of exercise HR. It appears that its function was restricted to buffering cardioaccelerations because, during both the control and LPP exercise conditions, the set point was located close to the threshold pressure of the pressure-response curve (see Fig. 2). At rest, in contrast, the set point coincided with the midportion of the operational pressure range. Accordingly, the reflex may modulate both cardioaccelerations and cariodecelerations in this condition. Whether or not this shift in the set point is related to exercise-induced changes in the interplay between sympathetic and parasympathetic control of the heart-beat frequency (cf. Robinson *et al.* 1966) remains to be settled.

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